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Application No. 10/665,188
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REMARKS

Currently pending claims 10-12 and 20-24 have been finally rejected as obvious over a newly cited Korean Patent Application to Kim et al. (KR2001098716A), alone or in combination with Carlsson et al. (US 6,117,857). Claims 22 and 24 have been objected to for informalities.

Applicant requests amendment to claims 22 and 24, and to withdrawn claims 8 and 26, to place these claims in proper Markush group format. Furthermore, Applicant requests amendment to claims 10 and 20, and to withdrawn claim 1, to add an additional claim limitation reciting that the mammalian amniotic membrane was subjected to only one freezing step during preparation of the extract. Applicant submits that this amendment is supported in the specification at least in Example I, pp. 11-12. Thus, no new matter has been added.

The Applicant's comments and arguments as to the rejections are given in the following Remarks. The rejections are respectfully traversed and reconsideration is requested.

Applicant has amended the withdrawn claims where appropriate (as required by MPEP § 821.04), using the claim identifier (Withdrawn/Currently Amended), further to the restriction requirement and Applicant's previous request that, when allowable subject matter is indicated, the remaining, withdrawn claims be rejoined as being directed to the extract of claim 20 *in a kit* (Group IV), a *method of making* the extract of claim 20 (Group I) and a *method of use* for the composition of claim 10 (Group III).

Applicant's amendment and cancellation of certain rejected claims is not to be construed as an admission that the Examiner's rejections were proper. The Applicant continues to believe that

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the rejected claims are described in and enabled by the specification and not obvious over the prior art as previously argued. The indicated claims have been amended for the sole purpose of advancing the case to allowance. The Applicant reserves the right to file a continuing application to continue the prosecution of the rejected claims as originally filed.

Rejections under 35 U.S.C. § 103(a)

Currently pending claims 10-12 and 20-24 have been rejected for obviousness over Kim et al. (KR2001098716A), alone or in combination with Carlsson et al. (US 6,117,857). This rejection is respectfully traversed and reconsideration is requested.

The invention described and claimed in the instant application is directed to a novel formulation for the therapeutic components of amniotic membrane, e.g., human amniotic membrane, a pharmaceutical composition that includes a therapeutically effective amount of an amniotic membrane extract preparation (AMX) consisting essentially of a powdered form of a lyophilized amniotic membrane homogenate supernatant, which can be reconstituted in a pharmaceutically acceptable carrier and wherein the mammalian amniotic membrane was subjected to only one freezing step during preparation of the extract. This last property of the claimed amniotic membrane extract preparation is added herein as a limitation to pending claims 10 and 20 and to withdrawn claim 1 as indicated above, and no new matter is added thereby.

The particular properties and benefits of the claimed extract preparation are recited in the accompanying Declaration of the inventor, Dr. Emiliano Ghinelli, as follows (statement no. 5):

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> As it is based on an extract prepared from a homogenate supernatant, the novel amniotic membrane formulation of the invention has been rid of cellular and intracellular debris. Yet, as the mammalian amniotic membrane was subjected also to only one freezing step during preparation of my extract, all of the important therapeutic factors determined by others to be present in an amniotic membrane are also present in the formulation of the invention. These factors can not only be detected but also quantified. Furthermore, as AMX is a homogeneous powder, the extract can be reconstituted in a pharmaceutically acceptable carrier at the concentration desired for a particular application, e.g., as in the original membrane or several times more concentrated than the original membrane to treat diseases not treatable by others using previously known amniotic membrane preparations. Thus, the amniotic membrane extract formulation according to my invention has the healing properties of amniotic membrane tissue, but at an enhanced level, and can be used as described in the instant application without the need for costly surgery.

In the Office Action, at p. 4, the Examiner characterizes Kim et al. as follows:

> Kim et al. teach a pharmaceutical composition comprising human amniotic membrane extract made by the process steps of 1) freeze-drying (lyophilized) and pulverizing (powdered) amniotic membrane and 2) homogenizing the powdered amniotic membrane, followed by centrifugation to obtain homogenate supernatant (see p.3, paragraph 4 of translated version). Reconstitution step of the claimed invention would be inherently carried out in Kim et al's method step because the powdered amniotic membrane has to be reconstituted in a solution for homogenization and centrifugation.

With respect, Applicant submits that the Examiner has misunderstood the teachings of Kim et al. The accompanying Ghinelli Declaration at pp. 4-8 addresses the teachings of Kim et

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al., and the differences between those teachings and the invention, as follows:

8. In my opinion as one of skill in the use of amniotic membrane preparations, the products described in Kim et al. are not at all like the products claimed in my application. I believe that the Examiner has misunderstood the process taught in the Kim et al. application and, therefore, has not appreciated the major differences between the Kim et al. products and those of my invention.

9. Further to my statements in my earlier Declaration, where I pointed out that my novel formulation is "a pharmaceutical composition that includes a therapeutically effective amount of an amniotic membrane *extract* preparation (AMX) consisting essentially of a *powdered form* of a *lyophilized* amniotic membrane *homogenate supernatant reconstituted* in a pharmaceutically acceptable carrier," I would now like to point out that my method of preparing my extract preparation *includes only one freezing step*. I will next explain the importance of this statement.

10. The mammalian amniotic membrane (amnion) is well-known for showing powerful and interesting healing properties and for containing a long list of therapeutically important factors. Processing the amnion for therapeutic use so that the critical healing factors are preserved has been problematic. I have determined, however, that an active and stable amniotic membrane extract *can* be prepared if the tissue is processed quickly and with care and is subjected to only one freezing step.

Mammalian tissue isolated from the mammalian body immediately starts a process of autolysis as cell degradation begins and proteolytic enzymes are released. The longer the time taken for the preparative procedure, the longer is the exposure to the autolysis process. In addition, many thermal jumps or changes in temperature, either cooling or warming jumps, accelerate these destructive processes. I am well-aware of these issues and so developed my preparative procedure accordingly.

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Referring now to Example I of my application, pp. 11-12, it can be seen therein that from the time of removal of the amniotic membrane from the pregnant woman who has just been delivered of her baby, through the homogenization and centrifugation steps, all procedures in my extraction process are carried out at approx. 4 °C (i.e., there is no freezing step). It is not until my homogenate supernatant is collected and divided into aliquots that it is quickly frozen (the only freezing step) and then kept in the frozen state until the extract material is "lyophilized," which means that the extract is maintained in its frozen state (in a small aliquot or in a frozen shell on the inside of a lyophilization bottle) while being evaporated to dryness under vacuum. The product of this process is a "powder" (see p. 12, line 14) which can be stored essentially indefinitely before being reconstituted for a specific use.

I emphasize that there is only one freezing step in this procedure and that my preparation is never thawed after that freezing step until the extract powder is produced. My preparation procedure protects important factors in the amnion in sufficient amount that their concentrations can be quantified.

11. The process of Kim et al., as indicated at the place analyzed by the Examiner (p. 3, paragraph 4 of the translated version), is very different. After isolation and washing, the Kim et al. amnion was placed in a stock solution, frozen (for the *first freezing step*) and "dried." This could not mean "dried" as in "freed from liquid," however, as in the next series of steps, the frozen amnion is "pulverized" using a mortar (and, presumably, a pestle), an activity that will substantially raise the temperature of the amnion - by the way; "homogenized"; and then "centrifuged" (for a very long time at a low speed) with the "supernatant" being isolated, which means liquid was present, even if frozen, when the amnion material was "pulverized." The collection of a supernatant means that the material being processed *must* be liquid at this point, and this liquid is the original "stock solution." The Examiner is in error when he states that this could be considered a "reconstitution step."

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The last lines of this paragraph indicate that the isolated and filtered Kim et al. supernatant is the material used for treatment without further "reconstitution." It is indicated earlier in the application (at p. 2, third paragraph from the bottom, last sentence of the translated version) that the filtered amniotic extract also can be "dried," which probably means freeze-dried, and pulverized. This would be the *second freezing step* in the Kim et al. process, and, thus, if carried out, would expose the Kim et al. extract to an *extra period of self-destruction time* (autolysis) compared to my preparative method in order to reach a "powdered" form.

12. The Kim et al. product has not been analyzed for specific protein content. Referring to the top of p. 2 in the translated version, the list of drawings recites no protein analysis steps. Proteins that *might* be present in the Kim et al. extract are discussed in the 2nd paragraph on p. 3 of the translation. However, this discussion relates to the amnion *before* the Kim et al. processing steps and is *only theoretical* in regard to the extract itself. It is my belief that, given the Kim et al. processing steps, it is highly unlikely that specific proteins *could* be quantified in this "extract" in a repeatable manner.

In contrast, as mentioned above, I have been able to quantify the concentration of a number of specific factors in my reconstituted extract. I have attached hereto the results of assays recently carried out on samples of my amniotic membrane extract (AMX) prepared as described in the instant application. Western blot analysis revealed proteins having an apparent MW consistent with the presence of fibronectin, NGF, BDNF and NT-3. ELISA tests specifically detected NGF levels at 8.4 pg/mL, TGF-α levels at 15.4 pg/mL, NT-3 levels at 25.05 pg/mL and IL-1ra levels at 851.11 pg/mL.

13. Therefore, given that, as I have shown, I have produced a product in which the important therapeutic factors of the amnion not only are still present but also can be quantified and, thus, administered to a patient in an amount appropriate for a specific therapy and given that Kim et al. have shown no ability to

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quantify any therapeutic factors that might remain in their product, it is my opinion as one of skill in the art that the "extract" disclosed in Kim et al. is completely different from my amniotic membrane extract (AMX).

Applicant submits that, when the teachings of Kim et al. are properly understood, it can be seen that the Examiner has not made a *prima facie* case of obviousness as the Examiner has not shown how one of ordinary skill, reviewing Kim et al., would arrive at the Applicant's invention absent hindsight use of the *Applicant's* teachings. It is the Applicant's position that the teachings of Kim et al., in fact, teach away from the claimed invention. Given the long extraction procedure taught by Kim et al., with its numerous cycles of freezing and thawing, there is no hint that the extract, to be viable, needs to be treated as the Applicant teaches, gently and with *only one freezing step* during the extraction process. Thus, the teachings of Kim et al., either alone or in combination with other references, cannot make obvious the invention as claimed in the instant application.

Claims 11 and 12 have been rejected as obvious over Kim et al. in view of Carlsson et al. (US 6,117,857). This rejection is respectfully traversed and reconsideration is requested. Applicant has described above the deficiencies of Kim et al. in making obvious the claimed invention. These deficiencies are not cured by a combination of Kim et al. with Carlsson et al. Thus, Applicant submits that the combination of Kim et al. with Carlsson et al. neither teaches nor fairly suggests all the limitations of the indicated claims and the rejection over this combination for obviousness is overcome.

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For the reasons indicated above, Applicant submits that all pending claims are in condition for allowance and such action is requested.

The Examiner is strongly encouraged to telephone the undersigned attorney to discuss any matter that would expedite allowance of the present application.

Respectfully submitted,

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